British Heart Journal, 1979, **41**, 133-138

Recurrence of myocardial infarction in an exercising population[1]

ROY J. SHEPHARD
From the Department of Preventive Medicine, University of Toronto, Toronto, Ontario, Canada

SUMMARY The Ontario Multi-Centre Exercise-Heart Trial is making a prospective study of 751 male subjects following well-documented episodes of myocardial infarction. Comparison is here made between the 50 participants who sustained a recurrence of their myocardial infarction, and the 701 participants who did not. Reinfarction was a little more likely with a history of multiple previous infarctions, but was unrelated to such indicators of infarct severity as symptoms, electrocardiographic abnormalities, enzyme changes, cardiac arrest, arrhythmia, or minimum systolic blood pressure. Features noted on admission to the trial, which may have an adverse effect, include smoking history and related symptoms, residual disability, shortness of breath, and angina of effort. The main physiological warning sign was a low and decreasing cardiac output at a submaximal work load, with a compensatory widening of arteriovenous oxygen difference. With the possible exception of exercise non-compliance, none of the adverse findings is sufficiently consistent to be of value when advising individual patients.

Previous work (Shephard, 1979; Kavanagh and Kennedy, 1977) has indicated that traditional 'coronary risk factors' are modified after infarction, particularly if the patients concerned are participating in a vigorous, exercise-centred rehabilitation programme. Given a recurrence rate of up to 4 per cent per annum, it would increase the safety of rehabilitation programmes if those patients with an above average risk of a further coronary event could be identified. Unfortunately, there are at present few clues to the detection of such individuals (Shephard *et al.*, 1977; Shephard, 1979).

The Ontario Multi-Centre Exercise-Heart Trial (Rechnitzer *et al.*, 1975) has now followed 50 of its 751 patients to the point of reinfarction. The opportunity has now been taken to compare these patients with the other participants in terms of (i) characteristics of the primary episode, (ii) clinical features on admission to the trial, and (iii) physiological responses to exercise, followed prospectively.

Subjects and methods

The subjects were 751 patients enrolled in the Ontario Multi-Centre Exercise-Heart Trial[1]; this has as its prime purpose a comparison of vigorous endurance activity and light recreation in the treatment of 'post-coronary' patients. Initial selection criteria are detailed elsewhere (Rechnitzer *et al.*, 1975). In brief, patients 54 years or younger were admitted to the trial 3 to 12 months after a myocardial infarct proven by 2 of 3 criteria (typical history of chest discomfort, serial electrocardiographic abnormalities typical of a transmural or subendocardial infarction, and typical changes in serum levels of AST (SGOT) or CK). Specific grounds for exclusion from the study included heart failure, a diastolic pressure in excess of 110 mmHg, insulin-dependent diabetes, orthopaedic disabilities, and gross abnormalities of pulmonary function ($FEV_{1.0}/VC < 60\%$).

After recruitment and clinical examination, subjects were allocated in a stratified random fashion to either a high intensity endurance exercise regimen or a low intensity recreational exercise programme. Both groups attended the rehabilitation centres regularly, and referring physicians received standardised advice on diet and other aspects of 'lifestyle'.

Detailed physiological tests were carried out on admission, and at 6 months, 12 months, 2, 3, and 4 years after recruitment. When patients were receiving propranolol or similar medications, the responsible clinician was approached one week before exercise testing, and asked to agree to a graded withdrawal of the drug. In a few subjects, this was deemed inadvisable, and at various points in the study it was necessary to test 5 to 7 patients who

[1]Ontario Multi-Centre Exercise-Heart Trial.

Principal investigators: G. Andrew, C. Buck, D. Cunningham, N. Jones, T. Kavanagh, N. Oldridge, J. C. Parker, P. Rechnitzer, S. Sangal, R. J. Shephard, J. Sutton, and M. Yuhasz.
Associate investigators: F. Berkman, P. Demers, R. Fowlis, P. Milos, B. Morton, P. Taylor, and R. Timming.

Received for publication 13 November 1978

were receiving treatment by beta-blocking drugs. The influence of such treatment on the test results is discussed where appropriate.

CLINICAL DATA

All clinical information relating to the primary episode and the condition on admission to the trial was recorded in a predetermined objective format.

PHYSIOLOGICAL TESTS

Lung volumes were determined by standard Stead-Wells spirometers with lightweight bells.

Exercise testing was carried out on electrically-braked bicycle ergometers, using a three-load progressive submaximal procedure; 6 to 8 minutes were allowed per test stage, the final loading being adjusted to a heart rate corresponding to 75 per cent of maximum oxygen intake.

Oxygen consumption, carbon dioxide output, and ventilatory measurements were made by a standard open-circuit technique (Shephard, 1977). Cardiac output and related measurements were obtained by the rebreathing technique of Jones and his associates (1975). Particular attention was directed to the standardisation of techniques between co-operating laboratories (Jones and Kane, 1979).

Results

(1) CHARACTERISTICS OF THE PRIMARY EPISODE[1]

(a) *Chest pain*

In those remaining free from recurrence during the prospective study, the primary episode had given rise to no chest pain in 11 subjects (1·6%), slight pain in 92 (13·3%), and severe pain in 587 (85·1%); no data were available for 11 subjects. In the 50 patients who developed a further infarction, symptoms were no more severe, 7 cases showing slight pain (14%) and 43 (86%) severe pain.

(b) *Diagnostic electrocardiographic abnormalities*

Six subjects without a recurrence (0·9%) showed no diagnostic electrocardiographic abnormalities, and in a further 56 (8·1%) changes were rated as 'borderline', leaving 627 (91·0%) with clearly diagnostic electrocardiograms and 12 subjects where electrocardiographic reports were not available. The proportion of cases with clear-cut electrocardiographic abnormalities (46/49, 93·9%) was insignificantly greater in those sustaining a recurrence.

(c) *Serum enzyme changes*

Enzyme data were available for 713 subjects (666 without, and 47 with a recurrence of infarction). Of those remaining free from infarction, enzyme changes were absent in 33 (5·0%), marginal in 55 (8·3%), and diagnostic in 578 (86·7%). Of those patients who had a recurrence, 5 patients (10·6%) showed no change, 1 (2·1%) a marginal change, and 41 (87·3%) a diagnostic increase.

(d) *Cardiac arrest*

One episode of cardiac arrest occurred in 36 of 689 patients (5·2%) free from recurrence, and 2 episodes or more occurred in 8 cases (1·2%). Such events were not significantly less frequent in those sustaining a recurrence (1 case, 2%, with a single episode of cardiac arrest).

(e) *Arrhythmia*

Occasional arrhythmia was observed in 196 of 683 subjects (28·7%) without recurrence, and frequent arrhythmia was encountered in 68 (10·0%). The occurrence of arrhythmia was very similar in those with a recurrence (15/49, 30·6%, had occasional arrhythmia and 5/49, 10·2%, frequent arrhythmia).

(f) *Minimum systolic blood pressure*

The mean minimum recorded systolic blood pressure was almost identical in those without (106·6 ± 2·98 mmHg) and those with a recurrence (105·8 ± 1·97 mmHg).

(g) *Number of previous infarctions*

Details of previous history were available for 689 patients without a recurrence during the period of observation: 52 (7·5%) had had 1 earlier infarct, 2 (0·3%) 2 previous infarcts, and 2 (0·3%) 3 previous infarcts. Proportions were slightly ($0·1 > P > 0·05$) higher for those developing a recurrence during the study (5 cases, 10%, with 1 infarct, 1 case, 2%, with 2 infarcts, and 1 case, 2%, with 3 infarcts).

(2) CLINICAL FEATURES ON ADMISSION TO THE TRIAL[1]

(a) *Smoking history and cardiorespiratory diseases*

The proportion of continuing smokers among those free from recurrence (248/696, 35·6%) was much as in other studies of post-coronary patients (Coronary Drug Project Research Group, 1975; Kavanagh *et al.*, 1977); 386 (55·4%) of 696 had stopped smoking, and 62 (8·9%) had never smoked. Proportions of smokers were marginally higher ($0·1 > P > 0·05$) among those sustaining a recurrence: 24 (48%) of 50 continued to smoke, and 24 (48%) were previous smokers.

[1]Data were not always available for all 701 cases without a recurrence or for all 50 cases with a recurrence.

Classifying subjects by the reported depth of smoke inhalation, 62 of 692 (8·9%) of those without recurrence noted 'slight' inhalation, 233 (33·7%) 'moderate' inhalation, and 295 (42·6%) 'heavy' inhalation. Of those with a recurrence, there was a slight suggestion ($0·2 > P > 0·1$) that more were reporting 'heavy' inhalation (27/50, 54%), but proportions with 'moderate' (15/50, 30%) and 'slight' inhalation (4/50, 8%) were much as in those without recurrence.

Probably because of its association with smoking, there was also a slight indication ($0·2 > P > 0·1$) that prognosis was affected by an initial history of wheezing. Of 698 without a recurrence, 143 (20·5%) experienced occasional wheezing, and 18 (2·6%) were wheezing most of the time. Of 49 with a recurrence, 15 (30%) were wheezing most of the time.

Other chest conditions also had a slight relation to prognosis. Haemoptysis was recorded in 3 patients (6%) with a recurrence, compared with 15 cases (2·2%) in those free from recurrence ($0·1 > P > 0·05$). Phlegm was produced on most days by 8 (16%) of those with a recurrence, compared with 65 (9·3%) of the remainder (699); winter sputum and/or sputum for 3 months of the year was likewise recorded in 5 subjects (10%), compared with 48 (6·9%). The combined χ^2 (2 degrees of freedom) for sputum production was 3·34 ($0·2 > P > 0·1$).

(b) *Activity and employment history*

When first seen, a small majority of those who remained free from recurrence were less active than before their infarction (354/699, 50·6%). In those with a recurrence (34/50, 68%) the proportion inactive was significantly greater ($0·02 > P > 0·01$). The reported daily walking distance was allocated to 1 of 3 categories (< 1 mile, 76/697, 10·9%; 1 to 3 miles, 162/697, 23·2%; > 3 miles 459, 65·8%); there was a statistically insignificant suggestion that those with a recurrence favoured the two lower categories of exercise (< 1 mile 6/50, 12·0%; 1 to 3 miles, 16/50, 32·0%; > 3 miles/day, 28/50, 56·0%).

The proportions continuing with their old job were rather similar in those without (515/699, 73·7%) and those with (34/50, 68·0%) a recurrence, but there was a slight but statistically insignificant suggestion of a change to part-time work in those with a recurrence (5/50, 10·0% compared with 51/699, 7·3%). Further, more of those sustaining a recurrence were engaged in light work (30/50, 60%) than were those who remained free from recurrence (333/699, 47·6%) ($0·1 > P > 0·05$).

The group with recurrent infarction contained more subjects engaged in commerce and financial activities than the group with no recurrence (38·0% vs. 17·7%, $P < 0·001$), and fewer subjects engaged in professional and managerial work (16·0% vs. 47·2%, $P < 0·001$). Work involving a combination of walking and lifting was also possibly a little more common ($0·2 > P > 0·1$) in those sustaining a recurrence (9/50 18%) than in those who did not (77/701, 11·5%).

Shortness of breath on exertion was reported by 41 (82%) of 50 with a recurrence, but by only 282 (39·4%) of 698 free from reinfarction, a highly significant difference ($P < 0·001$). Differences were apparent at all levels of dyspnoea (during brisk level walking, 28% versus 11%, when ascending a slight gradient, 38% versus 22%, and more severe grades of dyspnoea, 16% versus 6·7%).

(c) *Effort angina*

The proportion of the sample free from angina was similar in those who developed a recurrence (24/50, 48%) and in those who did not (356/697, 51·1%). However, those without a recurrence had fewer attacks during exercise, and more attacks at other times. Respective figures were for uphill or brisk walking 110 of 697 (15·8%) vs. 14 of 50 (28·0%), for level walking (sum of two categories) 62/697 (8·9%) vs. 5/50 (10·0%), and for other types of angina 169/697 (24·2%) vs. 7/50 (14·0%). The combined χ^2 for 3 degrees of freedom was 6·42 ($0·1 > P > 0·05$).

Neither the site of reference nor the duration of angina was helpful in distinguishing those who developed a recurrence of their infarction. Glyceryl trinitrate was taken by 11 (22·0%) of 50 with a recurrence, compared with 125 (18·8%) of 694 without. Calf pain on ordinary level walking was reported by 3 (6·0%) of 50 who had a recurrence, compared with 38 (5·4%) of 699 without recurrence.

(d) *Personality*

The proportions classed as having a type A personality (35/50, 70·0%, vs. 492/701, 70·2%) were very similar in those with and those without a recurrent infarction.

(3) PHYSIOLOGICAL RESPONSES

(a) *Lung volumes*

Initial spirometric values were not significantly less good in those sustaining a recurrence ($FEV_{1.0}$ 3·19 ± 0·18 vs. 3·35 ± 0·68 1 BTPS, FVC 4·19 ± 0·81 vs. 4·26 ± 0·76 1 BTPS).

(b) *Respiratory response to exercise*

For the purpose of comparing those with and without a recurrence of infarction, all data were stan-

Table 1 *Respiratory variables on entry to the study (E) and at 6, 12, 24, 36, and 48 months: comparison between data for patients with and without a recurrence of their infarction*

Variable and time (m)	*No recurrence*	*Recurrence*
V_D/V_T		
E	0·22± 0·07	0·23± 0·05
6	0·21± 0·08	0·18± 0·06
12	0·21± 0·07	0·27± 0·10*
24	0·22± 0·07	0·28± 0·06*
36	0·21± 0·06	—
48	0·26± 0·07	—
P_{aO_2} (mmHg)		
E	87·4 ± 8·2	89·9 ± 8·3
6	88·1 ± 7·7	86·6 ± 8·3
12	87·7 ± 8·3	85·3 ± 4·7
24	87·3 ± 8·2	75·7 ± 7·9*
36	89·4 ± 7·3	—
48	85·2 ± 6·7	—
$P_{(A-a)O_2}$ (mmHg)		
E	21·8 ±10·1	18·6 ± 9·7
6	20·3 ± 7·7	21·3 ±10·1
12	21·6 ± 8·0	22·2 ±10·2
24	20·1 ± 8·3	26·6 ± 6·8
36	17·7 ± 7·8	—
48	20·8 ± 5·9	—
Gas exchange ratio (R)		
E	0·94± 0·11	0·90± 0·11*
6	0·94± 0·10	0·89± 0·09*
12	0·95± 0·09	0·89± 0·08*
24	0·93± 0·10	0·89± 0·09
36	0·94± 0·12	—
48	0·92± 0·09	—

Note: Data expressed as mean ± SD, standardised to a $\dot{V}O_2$ of 1·25 l/min STPD. Details of sample size and differences between patients receiving high and low intensity exercise (all statistically insignificant) are available on request.

Significance of difference between patients with and without a recurrence of infarction: *P < 0·05.

Table 2 *Cardiovascular variables on entry to the study (E) and at 6, 12, 24, 36, and 48 months: comparison between data for patients with and without a recurrence of their infarction*

Variable and time (m)	*No recurrence*	*Recurrence*
Cardiac output (l/min)		
E	11·2± 2·3	10·8± 1·9
6	11·0± 1·9	10·2± 2·1*
12	11·1± 1·8	9·9± 2·0*
24	11·1± 1·6	10·3± 2·1
36	11·3± 2·6	
48	10·2± 1·1	
Stroke volume (ml)		
E	95·0±24·4	91·9±24·0
6	95·5±21·5	89·4±22·8
12	96·3±20·9	87·5±22·5
24	96·9±16·6	97·0±19·1
36	100·1±19·5	
48	92·0±22·3	
Arteriovenous oxygen difference (ml/l)		
E	116 ±23	119 ±22
6	117 ±20	127 ±31*
12	115 ±19	131 ±29**
24	115 ±19	121 ±14
36	114 ±20	
48	125 ±13	
Heart rate (bpm)		
E	119·3±16·9	118·9±15·0
6	115·8±15·9	115·3±13·0
12	116·5±16·6	113·7±13·7
24	114·6±15·2	108·0±16·4
36	112·8±18·0	
48	112·1±17·2	

Note: Data expressed as mean ± SD, standardised to a $\dot{V}O_2$ of 1·25 l/min STPD. Details of sample size and differences between patients receiving high and low intensity exercise (all statistically insignificant) are available on request.

Significance of difference between patients with and without a recurrence of infarction: *P < 0·05 **P < 0·01.

dardised by interpolation to a common oxygen consumption of 1·25 l per min STPD.

The majority of the respiratory measurements (respiratory minute volume, breathing rate, tidal volume, and alveolar ventilation) showed no differences between the groups. However, there were slight indications of a high dead space/tidal volume ratio, a low arterial oxygen pressure, an increased alveolar-arterial oxygen pressure gradient, and a low gas exchange ratio in those sustaining a reinfarction. With the exception of the low respiratory gas exchange ratio, these differences became more obvious as the period of observation was extended and the date of reinfarction was approached (Table 1).

(c) *Cardiac response to exercise*

The initial exercise cardiac output tended to be low in those patients who later had a recurrence of their infarction (Table 2). This difference became statistically significant at 1 year. The available data suggest that a decrease of stroke volume rather than heart rate was responsible. There were compensatory increases of arteriovenous oxygen difference, significant at 6 and 12 months of observation.

Exclusion of the few patients who were receiving beta-blocking drugs at the time of testing made little difference to the overall results. Thus, the mean heart rate of the patients without a recurrence dropped from 119·8 ± 15·7 (on entry) to 113·6 ± 14·3 (at 2 years) in the high intensity endurance group, and from 119·4 ± 17·6 (on entry) to 116·3 ± 15·9 (at 2 years) in the low intensity recreational group. Corresponding figures for those developing a recurrence on entry to the trial, and at the last test before reinfarction, were as follows: 122·6 ± 14·0 and 115·2 ± 14·7 (high intensity endurance group) and 117·4 ± 17·0 and 111·5 ± 17·7 (low intensity recreational group). There was no evidence that the abnormal function of those who had a recurrent infarction was the result of an unusually high proportion of patients treated by beta-blocking agents

Discussion

GENERAL CONSIDERATIONS

Perhaps the most striking feature of this survey is the similarity of patients who reinfarct and those who do not. While our sample undoubtedly includes some patients who had a slow, progressive extension of their disease, in many subjects the second infarction, like the first, was a sudden event, with little clinical or physiological warning. The latter pattern of recurrence is particularly likely in patients receiving exercise rehabilitation, since by selection they tend to be those with a less severe initial episode and a relatively complete restoration of function.

CHARACTERISTICS OF INITIAL EPISODE

The only clue to the likelihood of reinfarction is provided by a history of other previous infarctions. The other features examined (symptoms, electrocardiographic abnormalities, enzyme changes, cardiac arrest, arrhythmia, and minimum systolic blood pressure) might all be expected to relate to the severity of infarction, but nevertheless do not seem to modify subsequent prognosis. There are two possible explanations of this: (i) the referral process and criteria for admission to the multicentre trial may sort out a uniform type of patient, 'suitable' for exercise, who have had an infarction of less than average severity, and (ii) the prognosis may be determined more by residual function than by the characteristics of the previous acute episode.

CLINICAL FEATURES ON ADMISSION TO TRIAL

A previous report (Shephard *et al.*, 1977) noted a number of adverse characteristics. The most important was exercise non-compliance, and others included persistent smoking, angina, ventricular aneurysm, enlarged heart, multifocal ventricular premature beats, exercise ST segment depression, and a serum cholesterol 6·9 mmol/l or more ($\geqslant$ 270 mg/100 ml).

The present study gives limited support to the importance of smoking history ($0{\cdot}1 > P > 0{\cdot}05$) and related symptomatology ($0{\cdot}2 > P > 0{\cdot}01$). The adverse influence of residual disability ($0{\cdot}02 > P > 0{\cdot}01$), shortness of breath ($P < 0{\cdot}001$), and angina of effort ($0{\cdot}1 > P > 0{\cdot}05$) also suggest that exercise non-compliance (Shephard *et al.*, 1977) may be a risk indicator in part because it points to a poor residual myocardial function.

Other investigations (Rechnitzer *et al.*, 1979) suggest that a combination of personality type B, a blue-collar job, and vigorous exercise are associated with a poor prognosis. The present analysis also shows an effect of the type of employment on reinfaction rate ($P < 0{\cdot}001$). It is possible that those in professional and managerial posts are able to adopt a reduced pace of work after infarction, but this option is less available to those in commerce. It is also likely that the professional and managerial groups make greater changes of life style, particularly cessation of smoking, after infarction.

PHYSIOLOGICAL RESPONSES TO EXERCISE

Previous work (Shephard *et al.*, 1977; Shephard, 1979) suggested that one ominous sign of impending reinfarction was inability to develop a normal rise of systolic blood pressure during exercise.

The present study confirms the prognostic importance of a deteriorating myocardial function, the main adverse findings being a low cardiac output during sub-maximal exercise ($P < 0{\cdot}05$)[1], a widening of arteriovenous oxygen difference ($P < 0{\cdot}01$)[1], and poor matching of ventilation and perfusion ($P < 0{\cdot}05$)[1]. None of these indicators is clear cut, presumably because the reinfarctions are of at least two types: (i) a progressive pump failure, and (ii) a sudden ventricular arrhythmia.

Conclusion

The present report has uncovered a few further warnings of vulnerability to reinfarction in patients undergoing exercise rehabilitation. However, with the possible exception of exercise non-compliance (risk ratio 23, Shephard *et al.*, 1977), risk ratios are too low to be of great value in advising individual patients. The safety of exercise rehabilitation will thus continue to rest upon (i) a cautious initial exercise prescription, (ii) gradual progression of activity, and (iii) temporary restriction of activity if there are immediate adverse symptoms (Kavanagh and Shephard, 1973).

This research was funded in part by a Provincial Research Grant.

[1]Most significant difference noted during 4 years of observatton.

References

Coronary Drug Project Research Group (1975). Clofibrate and niacin in coronary heart disease. *Journal of the American Medical Association*, **231**, 360-381.

Jones, N. L., Campbell, E. J. M., Edwards, R. H. T., and Robertson, D. G. (1975). *Clinical Exercise Testing*. W. B. Saunders, Philadelphia.

Jones, N. L., and Kane, J. (1979). Quality control of physiological data in the multi-centre exercise-heart trial. *Medicine and Science in Sports*, **11**. (In press).

Kavanagh, T., and Shephard, R. J. (1973). The immediate antecedents of myocardial infarction in active men. *Canadian Medical Association Journal*, **109**, 19-22.

Kavanagh, T., Shephard, R. J., and Kennedy, J. (1977). Are the benefits of exercise in post-coronary rehabilitation an artefact of patient selection? *Cardiologia*, **62**, 84–85.

Rechnitzer, P. A., Cunningham, D. A., Sangal, S. A., Andrew, G., Buck, C., Jones, N. L., Kavanagh, T., Oldridge, N., Parker, J. O., Shephard, R. J., Sutton, J., and Yuhasz, M. S. (1979). The relationship of exercise to the recurrence rate of myocardial infarction in men—an interim report of the Ontarior Exercise Heart Collaborative Study. *Medicine and Science in Sports* (In press).

Rechnitzer, P. A., Sangal, S., Cunningham, D. A., Andrew, G., Buck, C., Jones, N. L., Kavanagh, T., Parker, J. O., Shephard, R. J., and Yuhasz, M. S. (1975). A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. A description of the experimental design. *American Journal of Epidemiology*, **120**, 358-365.

Shephard, R. J. (1977). *Endurance Fitness*, 2nd edn. University of Toronto Press, Toronto.

Shephard, R. J. (1978). Cardiac rehabilitation in prospect. In *Heart Disease and Rehabilitation. State of the Art*, ed M. Pollock. Houghton Mifflin, Pacific Palisades, California.

Shephard, R. J., Kavanagh, T., and Kennedy, J. (1977). Prognostic indices for ischaemic heart disease patients enrolled in an exercise-centred rehabilitation programme. *Cardiologia*, **62**, 141–142.

Requests for reprints to Professor R. J. Shephard, 150 College Street, Toronto M5S 1A1, Ontario, Canada.